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U.S. DEPARTMENT OF ENERGY | Office of Science

LIFE SCIENCES DIVISION E-NEWSLETTER

April 30, 2008

In this issue:

DOE scientific focus area notes

Low Dose Radiation Research

National Council for Radiation Protection Annual Meeting
Several Life Sciences scientists participated in the National Council for Radiation Protection annual meeting held in Washington, D.C., April 14-15**. Amy Kronenberg** was a member of the program committee, which was chaired by Antone Brooks, who has led scientific outreach for the OBER Low Dose program until his recent retirement. **Andrew J. Wyrobek** presented his research on the adaptive response and discussed the insights gained by pathway analysis of gene expression profiles. **Mary Helen Barcellos-Hoff** also spoke to the assembly of approximately 500 regulatory and agency representatives, interested public, and scientists. She discussed her research showing that non-targeted radiation effects can augment carcinogenesis in the mouse mammary gland. The meeting was concluded with remarks by agency representatives from NRC, EPA and DOE-OBER as to what it would take to affect the regulatory framework.

NSCOR Beta Tester for Google
Imaging bioinformatics has been a mainstay of **Mary Helen Barcellos-Hoff**'s low dose research since beginning a collaboration with **Bahram Parvin** under the auspices of a 1999 award from the DOE Low Dose Program entitled, "Bioinformatic Tools for Multiparametric Image Analysis". Now, the NASA Specialized Center of Research (NSCOR) project, headed by Barcellos-Hoff, has been selected by Google as one of the beta testers for the new Palimpsest project (http://blog.wired.com/wiredscience/2008/01/google-to-provi.html). **Sylvain Costes** initiated this collaboration with Google and gave a talk in April at Google headquarters discussing how his group has overcome some of the challenges in automatically identifying metadata in images, visualizing such datasets and batch processing their analysis. The talk aimed at identifying and potentially implementing similar visual and quantitative tools under the Palimpsest project. A large amount of the images generated by the NSCOR are currently uploaded onto Palimpsest and will serve as a template for data mining over gigantic dataset remotely. The Palimpsest project was started in April 2008 to provide a home for terabytes of open-source scientific datasets. The storage will be free to scientists and access to the data will be free for all in the near future.

Low Dose Program Represented
In her role of OBER Low Dose Chief Scientist, **Mary Helen Barcellos-Hoff** spoke to members of the Advisory Committee on Nuclear Waste and Materials Working Group on the effects of low radiation doses in Washington on April. She provided an overview of the program's objectives, scientific accomplishments to date and appraised them of how such data may affect the regulatory paradigm. In addition, she represented the program at a workshop organized by the World Nuclear Association's Director for Environment and Radiological Protection, Sylvain Saint-Pierre in Miami on April 11.

Mary Helen Barcellos-Hoff, 4/08

GTL-Genomics

PCAP and Electron Tomography of Microbial Cells

Electron tomography provides the technology to produce a three-dimensional map of sub-cellular structures at "molecular" resolution. This relatively new approach to structural biology is being used within the DOE-funded PCAP (Protein Complex Analysis Project) to understand details about the morphology of bacterial cells and ultimately to map out the locations of the major macromolecular complexes within the cells. This work is aimed at understanding mechanisms of metal reduction and the responses of the cells to stresses encountered when bacteria are used in bioremediation. Both conventional preparations, i.e. plastic-embedded, stained and sectioned specimens, and intact, frozen-hydrated cells are being studied. Sectioning and staining provide good contrast of structural features and make it possible to examine larger structures such as biofilms in order to understand the interrelationships among cells, while the unstained, frozen-hydrated cells have the best-preserved morphology of even the smallest details. Some examples from a section of a Desulfovibrio vulgaris biofilm are shown in figure 1 below. In these specimens, distinct areas of cells with good morphology can be seen along with other areas of cells that appear dead. The healthy cells are often accompanied by what seem to be strings of metal precipitates, which are presumably related to their metabolic activity. Further EM investigation will reveal more about the 3D nature of these precipitates and how they may be connected to individual cells. At higher magnification, a great deal of detail can be seen within these cells.

Frozen-hydrated samples require extra care in data collection since they are so sensitive to damage by the electron beam, and the contrast is much lower because they are unstained. However, the improvement in preservation of details provides advantages that, in principle, outweigh these disadvantages. Figure 2 is a section from the reconstruction of a dual-axis tomogram, recorded as the specimen was tilted around two orthogonal axes. This approach gives much more isotropic resolution and should aid in comparing densities seen within the cell to structures of macromolecular complexes expected to be in the cell. The ultimate goal is to map the locations of such complexes by comparison of the tomogram with a library of structures determined by single-particle electron microscopy in order to understand the potential interactions and function of these major molecular machines.

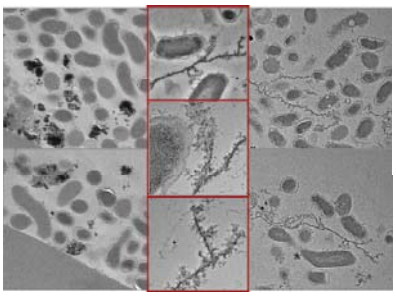


Fig. 1. Images of a plastic-embedded and sectioned Desulfovibrio biofilm. Areas are frequently fund where filaments and sheets of metal particles are interspersed among cells. Figure provided by Manfred Auer.

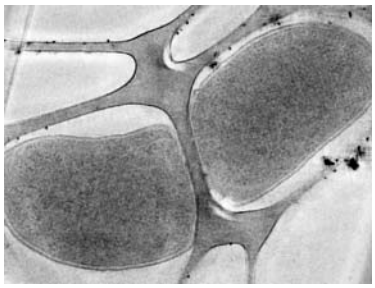


Fig.2. A thin slice (2.4 nm thick) from a tomographic, 3-D reconstruction of a frozen-hydrated Desulfovibrio cell suspended in a thin layer of buffer in a holey support film. The cell membranes as well as a wealth of internal detail are clearly visible. Figure provided by David Ball and Kenneth Downing.

The same approach is being used in studies of Caulobacter crescentus in a collaboration with Harley McAdams' group at Stanford, which is also funded as part of DOE's GTL program. Both of these projects include efforts in technology development, and a paper describing a novel approach to aligning the images in a tomographic tilt series was recently published by the Stanford and Berkeley groups: Fernando Amat, Farshid Moussavi , **Luis R. Comolli**, Gal Elidan, **Kenneth H. Downing** and Mark Horowitz Markov, Random field based automatic image alignment for electron tomography, *Journal of Structural Biology* , Volume 161, Issue 3, March 2008, Pages 260-275.

Continuing developments such as this alignment method are making electron tomography more productive and informative. In both projects scientists are now able to collect up to five tomograms in a one-day session on the microscope. Previously it would take about two days to process each tomogram; the new software eliminates about a day of the most manually intensive part of the processing. Further applications have already begun with scientists in the Life Sciences Division studying cellular mechanisms involved in the evolution of cancer and production of biofuels.
Kenneth Downing, 3/ 08

Nuclear Medicine

Symposium on Radiation Measurements and Applications
The next Symposium on Radiation Measurements and Applications (SORMA) will be held on the University of California, Berkeley campus June 2-5, 2008. The Organizing Committee's General Chair is **Stephen Derenzo** and **Bill Moses** is Co-Chair of this first West Coast meeting of SORMA. SORMA East will continue to be held every four years in its traditional home at the University of Michigan. With radiation detectors increasing in number, variety, and societal importance, the symposiums will alternate with SORMA West so that the forum will be available every two years.

The Berkeley symposium will offer a diverse and interesting program, encompassing the full breadth of ionizing radiation measurement applications and technologies, with both oral and poster presentations. The organizers have already accepted 320 abstracts and are expecting about 400 participants. Symposium Proceedings will appear as a special issue of a refereed journal.

The symposium is hosted jointly by the University of California, Berkeley and the Lawrence Berkeley and Lawrence Livermore National Laboratories. It is made possible by the generous support of the following sponsors: Department of Energy, National Nuclear Security Administration; Department of Homeland Security, Domestic Nuclear Detection Office (DNDO); the Department of Defense, Defense Threat Reduction Agency; and UC Berkeley support, coordinated through a joint National Science Foundation/DNDO Academic Research Initiative. More information:
http://www.lbl.gov/Conferences/SORMA/
CG, 4/08

Scientific news

Life Sciences Panel Highlights Breast Cancer Research Advances

On April 21 Science at the Theater hosted a dynamic panel of Berkeley Lab scientists highlighting breast cancer research advances related to susceptibility, early detection, prevention, and therapy — a biological systems approach to tackling the disease from the molecular and cellular levels, to tissues and organs, and ultimately the whole individual. **Joe Gray**, Life Sciences Division Director, explained how chromosomal abnormalities contribute to cancer and respond to gene-targeted therapies. **Mina Bissell**, former Life Sciences Division Director, approached the challenge of breast cancer from the breast's three dimensional tissue microenvironment and how the intracellular "conversation" triggers malignancies. **Mary Helen Barcellos-Hoff**, Deputy Director, Life Sciences Division, described what exposure to ionizing radiation can tell us about how normal tissues suppress carcinogenesis. The panel was moderated by Susan M. Love, breast cancer research pioneer, author, President and Medical Director of the Dr. Susan Love Research Foundation.

Photo courtesy: Roy Kaltschmidt/LBNL

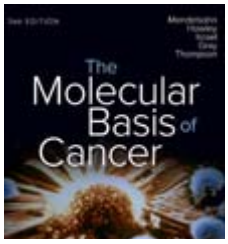
Science at the Theatre is organized by Berkeley Lab Friends of Science, an information and education resource provided by Berkeley Lab. The event took place at the Berkeley Repertory Theatre in Berkeley and was co-sponsored by the University of California at Berkeley, Chabot Space & Science Center, The Exploratorium, Lawrence Hall of Science, Osher Lifelong Learning Institute@Berkeley, and the Science Departments of Albany, Berkeley, and Oakland High Schools.
CG, 4/08; also in Today at Berkeley Lab, 4/14/08

Largest Reference for Scintillation Properties Now Available

A new website (http://scintillator.lbl.gov/) was put into operation that lists measured scintillation properties of many inorganic materials, and citations to the published papers in which the measurements were reported. This website, created by Life Scientists **Stephen Derenzo**, **Martin Boswell**, **Marvin Weber**, and **Kathleen Brennan**, is the largest reference for scintillation properties and is funded by the Department of Homeland Security. It currently has 242 entries relating to 130 different compounds. Properties include density, luminosity, emission wavelengths, decay times, and energy resolution for 662 keV gamma rays. It is intended for two main uses: (i) as a web-accessible reference to useful scintillation materials for detecting gamma rays for applications such as medical imaging, nuclear physics, and cargo screening, and (ii) as an aid in developing fundamental theories or empirical relations

between basic material properties and scintillation performance. New data will be added as they are published. During February and March 2008 it received 504 visits from 47 countries, and 167 of these were through the on-line encyclopedia www.wikipedia.com.
Stephen Derenzo, 4/08

New Edition of Gray's Cancer Reference Work



Joe Gray of Life Sciences is among the authors of the third edition of the acclaimed reference work, *The Molecular Basis of Cancer*, which has just appeared from Elsevier Publishing/Saunders. The new, full-color edition incorporates cutting-edge advances and the latest research to explore the scientific understanding of malignant transformation and the pathogenesis and treatment of cancer. With the book comes a bonus "Expert Consult Edition" website enabling full-text search and all the book's images downloadable for personal use, plus periodic updates. More details are available here: http://www.foyles.co.uk/display.asp?K=9781416037033&aub=Joe%20Craig&m=9&dc=14
Today at Berkeley Lab, 4/3/08

Life Scientist to Give 'New Directions' Talk

Life Sciences Postdoctoral Fellow **Mark LaBarge** (**Bissell** Lab) was selected to present his research at the "Future Leaders, New Directions" symposium. The gathering — part of the American Association for Cancer Research annual meeting — seeks to highlight the work of outstanding early-career scientists in cancer research. The symposium took place April 14 at the AACR annual Meeting in San Diego. Labarge spoke on how "Combinational Microenvironments and Cell-Cell Relationships Regulate Human Mammary Progenitor Cell Fate." Go here for more information (scroll down to "Future Leaders, New Directions"): http://www.aacr.org/home/scientists/associate-member-council/amc-at-the-annual-meeting.aspx
Today at Berkeley Lab, 4/8/08

Life Scientists Present at AACR Annual Meeting

Several Life Scientists participated in the American Association of Cancer Research (AACR) Annual Meeting, held in San Diego, April 12 – 16. **Joe Gray** chaired and presented in symposia on "Integrative Analysis of the Cancer Genome Omic" and "Pushing the State-of-the-Art in Ovarian Cancer", presenting on "The Ovarian Cancer Genome Atlas: Lessons from the Cancer Genome Atlas Projects". He also gave a talk at the 2008 Scientist Survivor Program. **Mina Bissell** presented her work on "Tumor Microenvironment", in a Meet-the-Expert session. **Judith Campisi** spoke at the educational session on "Cellular Senescence", which is a major focus of her research at LBNL. **Martha Stampfer** presented a poster that described some of her recent work on her lab's long-term project to develop in vitro (cell culture) model systems of normal human mammary epithelial cell (HMEC) behavior, and how normal properties are altered as the consequence of malignant transformation. **Roland Meier**, a Postdoctoral Fellow in **Mina Bissell**'s lab presented a poster on Neuroblastoma (NB) describing the potential role of CXCR4 in the malignant behavior of NB. Scientist **Paraic Kenny**, also of Bissell's lab presented his recent work on TACE, a protease which they have implicated as playing a crucial role in the production of pro-proliferative ligands of the Epidermal Growth Factor Receptor.

Postdoctoral Fellow **Zhi Hu** in **Joe Gray**'s lab, presented a talk and a poster titled, respectively, "Validating therapeutic targets on highly amplified chromosome regions in breast cancer " and "Cellular response of a novel PLK inhibitor in breast cancer cells"; Scientist **Eric Collisson** presented on "Co-purification and analysis of global gene expression and allele-specific copy number from a single microdissected FFPE sample in pancreatic ductal adenocarcinoma ". Presentations will be published in the 2008 Proceedings of the *AACR Research*.
CG, 4/08

Awards

Cancer Research Award Awarded

The 2008 AACR Team Science Award Winners received their Award on April 13, 2008 at the Opening Ceremony of the 2008 Annual Meeting. As mentioned in the March 31, 2008 E-Newsletter, the team was led by **Daniel Pinkel** of the Life Sciences Division. Members include **Joe Gray** and **Damir Sudar** of Life Sciences and Robert Nordmeyer of Engineering, along with colleagues from UC San Francisco. The award honors the interdisciplinary team for their conception, implementation, and clinical application of pioneering comparative genomic hybridization techniques, which link tumor genomes to breast cancer outcomes. Photo courtesy: CG.

Recent publications (selected)

Eberling JL, **Jagust WJ**, Christine CW, Starr P, Larson P, **Bankiewicz KS**, Aminoff MJ. Results from a phase I safety trial of hAADC gene therapy for Parkinson disease. *Neurology* 2008 Apr 9 PMID: 18401019

> BACKGROUND: In a primate model of Parkinson disease (PD), intrastriatal infusion of an adeno-associated viral (AAV) vector containing the human aromatic L-amino acid decarboxylase (hAADC) gene results in robust gene expression. After gene transfer, low doses of systemically administered L-dopa are converted to dopamine in the transduced striatal neurons, resulting in behavioral improvement without the side effects typically associated with higher doses of L-dopa. These studies led to the initiation of a phase I safety trial. Here we report the findings for the first cohort of five patients. METHODS: Patients with moderate to advanced PD received

bilateral infusion of a low dose of the AAV-hAADC vector into the putamen. PET scans using the AADC tracer, 6-[18F]fluoro-L-m-tyrosine (FMT), were performed at baseline and at 1 and 6 months after infusion as an in vivo measure of gene expression. RESULTS: PET results showed an average 30% increase in FMT uptake (Ki(c)) in the putamen after gene transfer. Preliminary analysis of clinical data indicates a modest improvement, but absence of a control and the nonblinded analyses make interpretation difficult. CONCLUSIONS: Thus far, this gene therapy approach has been well tolerated and shows PET evidence of sustained gene expression. These initial findings demonstrate the safety of the therapy; higher doses of adeno-associated viral vector containing the human aromatic L-amino acid decarboxylase gene in the next cohort of patients may further increase dopamine production in the putamen and provide more profound clinical benefit.

Fowlkes CC, **Hendriks CL**, Keränen SV, **Weber GH**, Rübel O, **Huang MY**, Chatoor S, **DePace AH**, **Simirenko L**, **Henriquez C**, **Beaton A**, **Weiszmann R, Celniker S, Hamann B, Knowles DW, Biggin MD, Eisen MB**, Malik J. A quantitative spatiotemporal atlas of gene expression in the Drosophila blastoderm. *Cell* 2008 Apr 18;133(2):364-74 PMID: 18423206

To fully understand animal transcription networks, it is essential to accurately measure the spatial and temporal expression patterns of transcription factors and their targets. We describe a registration technique that takes image-based data from hundreds of Drosophila blastoderm embryos, each costained for a reference gene and one of a set of genes of interest, and builds a model VirtualEmbryo. This model captures in a common framework the average expression patterns for many genes in spite of significant variation in morphology and expression between individual embryos. We establish the method's accuracy by showing that relationships between a pair of genes' expression inferred from the model are nearly identical to those measured in embryos costained for the pair. We present a VirtualEmbryo containing data for 95 genes at six time cohorts. We show that known gene-regulatory interactions can be automatically recovered from this data set and predict hundreds of new interactions.

Downing , K. H. and Mooney, P. E. A charge coupled device camera with electron decelerator for intermediate voltage electron microscopy. *Review of Scientific Instruments* . 79, 043702 April 18 2008; DOI:10.1063/1.2902853

Electron microscopists are increasingly turning to intermediate voltage electron microscopes (IVEMs) operating at 300–400 kV for a wide range of studies. They are also increasingly taking advantage of slow-scan charge coupled device (CCD) cameras, which have become widely used on electron microscopes. Under some conditions, CCDs provide an improvement in data quality over photographic film, as well as the many advantages of direct digital readout. However, CCD performance is seriously degraded on IVEMs compared to the more conventional 100 kV microscopes. In order to increase the efficiency and quality of data recording on IVEMs, we have developed a CCD camera system in which the electrons are decelerated to below 100 kV before impacting the camera, resulting in greatly improved performance in both signal quality and resolution compared to other CCDs used in electron microscopy. These improvements will allow high-quality image and diffraction data to be collected directly with the CCD, enabling improvements in data collection for applications including high-resolution electron crystallography, single particle reconstruction of protein structures, tomographic studies of cell

ultrastructure, and remote microscope operation. This approach will enable us to use even larger format CCD chips that are being developed with smaller pixels. ©2008 American Institute of Physics

Chin L, **Gray JW**. Translating insights from the cancer genome into clinical practice. *Nature*. 2008 Apr 3;452(7187):553-63 PMID: 18385729

Cancer cells have diverse biological capabilities that are conferred by numerous genetic aberrations and epigenetic modifications. Today's powerful technologies are enabling these changes to the genome to be catalogued in detail. Tomorrow is likely to bring a complete atlas of the reversible and irreversible alterations that occur in individual cancers. The challenge now is to work out which molecular abnormalities contribute to cancer and which are simply 'noise' at the genomic and epigenomic levels. Distinguishing between these will aid in understanding how the aberrations in a cancer cell collaborate to drive pathophysiology. Past successes in converting information from genomic discoveries into clinical tools provide valuable lessons to guide the translation of emerging insights from the genome into clinical end points that can affect the practice of cancer medicine.

Karlsson, K. H., Radulescu, I., **Rydberg, B**. and Stenerlöw, B. Repair of Radiation-Induced Heat-Labile Sites is Independent of DNA-PKcs, XRCC1 and PARP. *Radiation Research.* 169, 506- 512 May 2008. PMID:18439038

Ionizing radiation induces a variety of different DNA lesions; in addition to the most critical DNA damage, the DSB, numerous base alterations, SSBs and other modifications of the DNA double-helix are formed. When several non-DSB lesions are clustered within a short distance along DNA, or close to a DSB, they may interfere with the repair of DSBs and affect the measurement of DSB induction and repair. We have shown previously that a substantial fraction of DSBs measured by pulsed-field gel electrophoresis (PFGE) are in fact due to heat-labile sites within clustered lesions, thus reflecting an artifact of preparation of genomic DNA at elevated temperature. To further characterize the influence of heat-labile sites on DSB induction and repair, cells of four human cell lines (GM5758, GM7166, M059K, U-1810) with apparently normal DSB rejoining were tested for biphasic rejoining after gamma irradiation. When heat-released DSBs were excluded from the measurements, the fraction of fast rejoining decreased to less than 50% of the total. However, the half-times of the fast (t(1/2) = 7-8 min) and slow (t(1/2) = 2.5 h) DSB rejoining were not changed significantly. At t = 0, the heat-released DSBs accounted for almost 40% of the DSBs, corresponding to 10 extra DSBs per cell per Gy in the initial DSB yield. These heat-released DSBs were repaired within 60-90 min in all cells tested, including M059K cells treated with wortmannin and DNA-PKcs-defective M059J cells. Furthermore, cells lacking XRCC1 or poly(ADP-ribose) polymerase 1 (PARP1) rejoined both total DSBs and heat-released DSBs similarly to normal cells. In summary, the presence of heat-labile sites has a substantial impact on DSB induction and DSB rejoining rates measured by pulsed-field gel electrophoresis, and heat-labile sites repair is independent of DNA-PKcs, XRCC1 and PARP.

Campisi J. Aging and cancer cell biology, *Aging Cell* 2008 Apr 7, PMID: 18331618

> There is increasing support for the idea that aging and cancer are intimately connected by the activity of specific genes and the cellular responses to potentially oncogenic insults. This Hot Topics review discusses some recently published articles that shed light on both the commonalities - and intricacies - of the cancer-aging relationship. These articles reveal the expected complexities, but also surprising conservation, in mechanisms that link cancer and aging.

Garcin ED, Hosfield DJ, Desai SA, Haas BJ, Björas M, Cunningham RP, **Tainer JA**. DNA apurinic-apyrimidinic site binding and excision by endonuclease IV. *Nature Structure & Molecular Biology* 2008 Apr 13 PMID: 18408731

> Escherichia coli endonuclease IV is an archetype for an abasic or apurinic-apyrimidinic endonuclease superfamily crucial for DNA base excision repair. Here biochemical, mutational and crystallographic characterizations reveal a three-metal ion mechanism for damage binding and incision. The 1.10-A resolution DNA-free and the 2.45-A resolution DNA-substrate complex structures capture substrate stabilization by Arg37 and reveal a distorted Zn(3)-ligand arrangement that reverts, after catalysis, to an ideal geometry suitable to hold rather than release cleaved DNA product. The 1.45-A resolution DNA-product complex structure shows how Tyr72 caps the active site, tunes its dielectric environment and promotes catalysis by Glu261-activated hydroxide, bound to two Zn(2+) ions throughout catalysis. These structural, mutagenesis and biochemical results suggest general requirements for abasic site removal in contrast to features specific to the distinct endonuclease IV alpha-beta triose phosphate isomerase (TIM) barrel and APE1 four-layer alpha-beta folds of the apurinic-apyrimidinic endonuclease families.

Markstein M, Pitsouli C, Villalta C, **Celniker SE**, Perrimon N. Exploiting position effects and the gypsy retrovirus insulator to engineer precisely expressed transgenes. *Nature Genetics* 2008 Apr; 40(4):476-83. PMID: 18311141

> A major obstacle to creating precisely expressed transgenes lies in the epigenetic effects of the host chromatin that surrounds them. Here we present a strategy to overcome this problem, employing a Gal4-inducible luciferase assay to systematically quantify position effects of host chromatin and the ability of insulators to counteract these effects at phiC31 integration loci randomly distributed throughout the Drosophila genome. We identify loci that can be exploited to deliver precise doses of transgene expression to specific tissues. Moreover, we uncover a previously unrecognized property of the gypsy retrovirus insulator to boost gene expression to levels severalfold greater than at most or possibly all un-insulated loci, in every tissue tested. These findings provide the first opportunity to create a battery of transgenes that can be reliably expressed at high levels in virtually any tissue by integration at a single locus, and conversely, to engineer a controlled phenotypic allelic series by exploiting several loci. The generality of our approach makes it adaptable to other model systems to identify and modify loci for optimal transgene expression.

Peng JC, **Karpen GH.** Epigenetic regulation of heterochromatic DNA stability. *Current Opinion Genetics and Development* 2008 Mar 25 PMID: 18372168

> In this review we summarize recent studies that demonstrate the importance of epigenetic mechanisms for maintaining genome integrity, specifically with respect to repeated DNAs within heterochromatin. Potential problems that arise during replication, recombination, and repair of repeated sequences are counteracted by post-translational histone modifications and associated proteins, including the cohesins. These factors appear to ensure repeat stability by multiple mechanisms: suppressing homologous recombination, controlling the three-dimensional organization of damaged repeats to reduce the probability of aberrant recombination, and promoting the use of less problematic repair pathways. The presence of such systems may facilitate repeat and chromosome evolution, and their failure can lead to genome instability, chromosome rearrangements, and the onset of pathogenesis.

Williams PT. Relationships between walking distance and percentiles of BMI in older and younger men. *British Journal of Sports Medicine* 2008 Apr 2 PMID: 18385193

> OBJECTIVE: To assess the relationships of weekly walking distance to body weight and waist circumference in elderly (age>/=75 years), senior (55</=age<75 years), middle-aged (35</=age<55 years), and younger men (18</=age<35 years old). DESIGN: Cross-sectional analyses of baseline questionnaires from 7,082 male participants of the National Walkers' Health Study. RESULTS: Standard regression analyses showed that BMIs were inversely and significantly associated with walking distance (kg/m2 per km/wk) in elderly (slope +/- SE: -0.032+/-0.008), senior (-0.045+/-0.005), and middle-aged men (-0.037+/-0.007), as were their waist circumferences (-0.091+/-0.025, -0.045+/-0.005, and -0.091+/-0.015 cm per km/wk, respectively), and that these slopes remained significant when adjusted statistically for reported weekly servings of meat, fish, fruit, and alcohol. However, percentile regression analyses showed that the declines in BMI per km/wk walked were greater at the higher than lower percentiles of the BMI distribution. In men ?75 years old the decline per km walked was 5.1-fold greater among the heaviest men (i.e., 90th BMI percentile, -0.100 kg/m2 per km/wk) than among the leanest men (i.e., 10th BMI percentile; -0.018 kg/m2 per km/wk). The differences in slope at the 90th compared to the 10th BMI percentile were 5.9-fold among men 55-74 years old and 6.7-fold among men 35-54 years old. Per km/wk walked, the declines at the 90th percentile of waist circumference were also greater than at its 10th percentile, and intermediate for percentiles in between. Whereas standard regression analyses suggest that the average declines in BMI per km/wk walked reported here are consistent with those reported previously per km/wk run in male runners 35-54 (-0.036+/-0.001 kg/m2 per km/wk) and >/=50 years old (-0.038+/-0.001 kg/m2 per km/wk), percentile regression analyses showed that when adjusted to the leaner body weights of the runners the declines per km walked were between 49% and 59% less for walkers than runners. CONCLUSIONS: Declines in BMI and waist circumferences with walking distance depend upon the percentile of the BMI distribution, with the decline per km walked being significantly greater among heavier men.

Auer M, Koster AJ, Ziese U, Bajaj C, Volkmann N, Wang DN, Hudspeth AJ. Three-dimensional Architecture of Hair-bundle Linkages Revealed by Electron-microscopic Tomography. *Journal of the Association for Research in Otolaryngology* 2008 Apr 18 PMID: 18421501

The senses of hearing and balance rest upon mechanoelectrical transduction by the hair bundles of hair cells in the inner ear. Located at the apical cellular surface, each hair bundle comprises several tens of stereocilia and a single kinocilium that are interconnected by extracellular proteinaceous links. Using electron-microscopic tomography of bullfrog saccular sensory epithelia, we examined the three-dimensional structures of basal links, kinociliary links, and tip links. We observed significant differences in the appearances and dimensions of these three structures and found two distinct populations of tip links suggestive of the involvement of different proteins, splice variants, or protein-protein interactions. We noted auxiliary links connecting the upper portions of tip links to the taller stereocilia. Tip links and auxiliary links show a tendency to adopt a globular conformation when disconnected from the membrane surface.

Veress AI, Weiss JA, **Huesman RH**, **Reutter BW**, **Taylor SE**, Sitek A, Feng B, Yang Y, **Gullberg GT**. Measuring Regional Changes in the Diastolic Deformation of the Left Ventricle of SHR Rats Using microPET Technology and Hyperelastic Warping. *Annals of Biomedical Engineering* 2008 Apr 24 PMID: 18437574

The objective of this research was to assess applicability of a technique known as hyperelastic warping for the measurement of local strains in the left ventricle (LV) directly from microPET image data sets. The technique uses differences in image intensities between template (reference) and target (loaded) image data sets to generate a body force that deforms a finite element (FE) representation of the template so that it registers with the target images. For validation, the template image was defined as the end-systolic microPET image data set from a Wistar Kyoto (WKY) rat. The target image was created by mapping the template image using the deformation results obtained from a FE model of diastolic filling. Regression analysis revealed highly significant correlations between the simulated forward FE solution and image derived warping predictions for fiber stretch (R (2) = 0.96), circumferential strain (R (2) = 0.96), radial strain (R (2) = 0.93), and longitudinal strain (R (2) = 0.76) ($p < 0.001$ for all cases). The technology was applied to microPET image data of two spontaneously hypertensive rats (SHR) and a WKY control. Regional analysis revealed that, the lateral freewall in the SHR subjects showed the greatest deformation compared with the other wall segments. This work indicates that warping can accurately predict the strain distributions during diastole from the analysis of microPET data sets.